CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20375/S012

ADMINISTRATIVE DOCUMENTS

MINUTES of TELECON

Date: June 9, 1998 **Time:** 10:00 - 10:20 PM **Location:** Parklawn; 17B-45

NDA: 20-375/S-012 **Drug Name:** Climara® (estradiol transdermal system) 0.1 mg/day and 0.05 mg/day

External Participant: Berlex Laboratories

Type of Meeting: Chemistry Advice

Meeting Chair: Dr. Marianne Mann **External Participant Lead:** Mr. Jeffrey Millington

Meeting Recorder: Mrs. Diane Moore

FDA Attendees:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)
Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

External Constituents:

[redacted]

June Bray - Director, Regulatory Affairs
Sharon Brown - Associate Director, Regulatory Affairs
Geoffrey P. Millington - Manager, Drug Regulatory Affairs

[redacted]

Mary Mathisen - Senior Regulatory Officer
Lisa Schnose - Product Support Engineer
Florence Wong - Director, Regulatory Affairs and Quality Assurance

Meeting Objectives:
To discuss the expiration dates on Climara® batches in reference to additional data submitted by Berlex and 3M Pharmaceuticals in the telefacsimiles dated June 3 and 5, 1998, respectively (see attached).

Discussion Points:

- the approval of the 24-month expiration date for the 0.1 mg/day system was based on actual data from the 0.05 mg/day and 0.1 mg/day systems; no actual data was provided for the 0.075 mg/day system; in order to extend the shelf life for the 0.1 mg/day strength system to a 36-month expiration date, actual stability data from three commercial batches must be reviewed

- although the use of the Femtran data for the third commercial batch strength, 0.1 mg/day, may be scientifically reasonable, there may be regulatory issues regarding this which should be addressed
    - to bridge the data from Femtran to support a 36-month expiration date for the Climara® 0.1 mg/day (higher strength) system, the manufacturing process for Femtran should be included in the review of the stability data for the Femtran product
- the 0.05 mg/day dose system is currently on backorder
- stability data for the 0.05 and 0.1 mg/day strengths are from ambient room temperature conditions, not from ICH conditions

Decisions reached:

- a partial supplement approval may be made on the basis of available data submitted to the DMF for the 0.05 and 0.1 mg/day transdermal systems; if additional 36-month stability data for the 0.1 mg/day strength system is acceptable, it can be submitted to the annual report
    - the 0.05 mg/day patch (lowest strength) can be released with a 36 month expiration date
    - the 0.075 mg/day transdermal system (middle dose) will have a 24 month expiration date
    - data from studies of the 0.075 mg/day strength system under ICH conditions must be provided to confirm that previous storage conditions are equivalent to ICH conditions
- stability data from the plant on the 0.1 mg/day transdermal system (highest strength) from a third commercial lot should be submitted by the end of June; if this is done, data from Femtran will not be necessary

Action Items:

	Item:	Responsible Person:	Due Date:
•	Complete CMC review for 0.05 and 0.1 mg/day strengths	Dr. Mitra	2 days
•	issue action letter	Ms. Moore	2 days
•	submit data on third commercial lot for 0.1 mg/day strength system	Berlex	end of June

/S/ 6/25/98
Signature, minutes preparer

/S/ 6/26/98
Concurrence, Chair

Post Meeting Addendum:

In a telephone conversation between Diane Moore and Mr. Geoffrey Millington, at Berlex on June 10, 1998, Berlex agreed to send, via telefacsimile, a copy of the 36-month stability data for the third batch of the 0.1 mg/day strength system as soon as it is available for the Agency to review for acceptability before submitting the data to the annual report.

drafted: dm/June 9, 1998/n2037560998
cc:
NDA Arch:
HFD-580
HFD-580/LRarick/MMann/MRhee/AMitra/DMoore/JMercier

Concurrence:
TRumble, AMitra, MRhee 06.11.98/MMann 06.17.98

Climara® 0.05 mg/day (3.9 mg/patch) - Analysis of Marketed Product Stability Data to Support a 36 Months Expiration Dating Period

This report presents the data analysis results for marketed product stability studies conducted on Climara® 0.05 mg/day (Estradiol Transdermal Patches, 3.9 mg/patch) to support an allowable expiration dating period of 36 months. The data used in the analysis have been generated on samples stored at Controlled Room Temperature ("R.T.") and ambient relative humidity for a period of 36 months. The data are provided in separate Stability Data Summaries (Attachment I) for the following studies;

12.5 sq cm Patches (3.9 mg/patch)	*Lot No.*
EST(3.9)-3	950472
EST(3.9)-4	950318
EST(3.9)-5	950346

These lots were produced with both rollstock coating and finished patch converting done at manufacturing facility, and provide the required three lots stored for the full term of the proposed expiry period. Statistical analysis of the data was done using the SAS Program provided by FDA for this purpose (written by Moh-Jee Ng, Division of Biometrics, March 9, 1992). The program was run on a PC using The SAS System for Windows, Release 6.12.

Additional enclosed attachments (Attachments II through V) provide the results of the separate analyses for Estradiol Content (% of label claim), and for Drug Release Rate at the 10, 45, and 180 minute test points for the currently marketed 3.9 mg/patch size. The format of the SAS program output has been modified somewhat for a more concise and readable presentation of the results.

The test data and SAS analysis output for all three lots of the 3.9 mg/patch size are also shown graphically for each of the four test attributes noted above. In each case, the Analysis of Variance results indicate that pooling of the lots to conduct a composite analysis is not warranted (ie., ***separate intercept:common slope*** or ***separate intercept:separate slope*** models must be used) thus graphs are presented for each attribute separately for each of the three lots being considered.

Based on the SAS data analysis output, the calculated maximum allowable expiry period is at least 60 months in all cases. Because the longest test interval for the currently available data is 36 months, this is the expiry period which will be assigned for the 0.05 mg/day (3.9 mg/patch, 12.5 sq. cm.) patch size under consideration.

The stability protocol for marketed product samples also includes testing for Chromatographic Purity and Adhesion Strength (test added March 1996). For the studies reported here, there were no impurities observed in the TLC chromatograms of any of the samples tested at each pull point and storage condition. There is currently only limited data available for the Adhesion Strength test, however results to date are well within the shelf-life specifications, showing some scatter in the data from point to point, but with no observable trends overall.

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